PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/20, 31/19, 31/195

A1

(11) Internati nal Publication Number: **WO 00/06125**

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/04874

(22) International Filing Date: 12 July 1999 (12.07.99)

(30) Priority Data:
MI98A001774 30 July 1998 (30.07.98) IT

(71) Applicant: ZAMBON GROUP S.P.A. [IT/IT]; Via della Chimica, 9, I–36100 Vicenza (IT).

(72) Inventors: GRASSANO, Alessandro; Via Volturno, 21, I–20052 Monza (IT). MARCHIORRI, Maurizio; Via Don Orsenigo, 11, I–22039 Valbrona (IT). DI TORO, Mauro; Via Vittorino Mandelli, 18/A, I–20050 Ronco Briantino (IT). CASTEGINI, Franco; Strada Gogna, 37, I–36100 Vicenza (IT).

(74) Agent: LONGONI, Alessandra; Zambon Group S.p.A., Corp. Patent & Trademark Dept., Via Lillo del Duca, 10, I–20091 Bresso (IT).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: FAST DISSOLVING IBUPROFEN CONTAINING COMPOSITIONS HAVING ANALGESIC ACTIVITY

(57) Abstract

An analgesic composition useful in the preparation of fast dissolving tablets is provided wherein the composition is the result of combining ibuprofen, arginine, linear PVP and an alkaline bicarbonate to which usual excipients for the preparation of tablet are added.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

FAST DISSOLVING IBUPROFEN CONTAINING COMPOSITIONS HAVING ANALGESIC ACTIVITY

****

The present invention relates to an analgesic composition for preparing fast dissolving tablets containing ibuprofen and arginine and the tablets made therefrom.

Ibuprofen is the International common name of the compound 2-(4-isobutylphenyl)-propionic acid, which is a known drug with analgesic, as well as anti-inflammatory and antipyretic, activity of broad diffusion.

In U.S. Patcnt No. 4,279,926 (SPA-Società Prodotti Antibiotici S.p.A.) ibuprofen salts with basic amino acids such as arginine and lysine have been described. To our knowledge only the lysine salt has been commercialised.

In U.S. Patent No. 4,689,218 (Zambon Group S.p.A.) effervescent compositions of ibuprofen containing arginine together with 20-30% by weight of bicarbonate and 25-40% by weight of sodium bitartrate have been described.

The described formulations are useful for preparing drinkable aqueous solutions.

In U.S. Patent No. 4,834,966 (Zambon Group S.p.A.) non-effervescent compositions are disclosed consisting, as a base, of a ternary mixture consisting of ibuprofen, 1.1 to 1.5 mol% arginine per mole of ibuprofen and sodium bicarbonate in a weight amount between 0.25 and 0.75 times the weight of ibuprofen.

These formulations are disclosed as very suitable for the preparation of granulates quickly soluble in water.

The administration of the so obtained aqueous solutions assures a fast analgesic effect which is achieved in about ten minutes.

Sachets containing the granulate of US 4,834,966 are on the market.

In some Countries, and in particular in the U.S.A., the preparations in the form of a sachet are not particularly appreciated by the public, who generally prefer the use of tablets in the treatment of conditions which need an analgesic drug.

The commercially available tablets containing ibuprofen do not have a particularly fast effect because they require about 30 minutes to completely dissolve and reach the blood stream.

In order to obtain a quick dissolution of the active principle, the present inventors tried preparing tablets starting from the ibuprofen-arginine-sodium bicarbonate ternary mixture of

the above mentioned U.S. Patent No. 4,834,966.

Unfortunately, it was impossible to obtain satisfactory results because the resulting tablets were too friable and subject to fragmentation during manufacturing and packaging.

Therefore, there was the problem to have available tablets having good workability and a fast dissolution so as to assure a prompt analgesic effect.

These results have been obtained thanks to a new mixture containing ibuprofen, arginine, linear polyvinylpyrrolidone (PVP) and a reduced amount of an alkaline bicarbonate.

Therefore, an object of the present invention is an analgesic composition comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen.

A further object of the present invention is a fast dissolution tablet comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen and including also normal excipients useful for the preparation of tablets.

Preferably ibuprofen is contained in amounts of from 100 to 400 mg/tablet, more preferably in amounts of 100, 200 mg/tablet, most preferably in an amount of 200 mg/tablet.

Arginine is preferably contained in an n amount from 1.1 to 1.3 moles per mole of ibuprofen and more preferably in an amount of 1.2 moles per mole of ibuprofen.

Linear PVP is preferably a PVP having an average K value, determined according to the method described in the U.S. Pharmacopoeia XXIII, of from 25 to 90, more preferably from 50 to 90, most preferably PVP K90. It is preferably used in an amount of from 2 to 8% by weight with respect to the weight of ibuprofen.

The alkaline bicarbonate is sodium and potassium bicarbonate and it is preferably used in an amount of from 7 to 10% by weight with respect to the weight of ibuprofen.

Within the present context the identity of the components and amounts thereof refer to the weight and identity of the starting materials used in preparing the composition. It is possible that during preparation of the composition and/or tablets, some interaction or reaction may

occur between two or more components. To the extent that such interaction or reaction occurs the present invention is intended to cover such occurrences.

Normal excipients useful in the preparation of the tablets include, but are not limited to: lubricants such as magnesium stearate, sodium stearyl fumarate and sodium benzoate; anti-adherents such as talc and polyethylenglycol; glidants such as colloidal silica; diluents such as dicalcium phosphate, cellulose (for example microcrystalline cellulose) and its derivative, carbohydrates and polyalcohols such as saccharose, xylitol and lactose; disintegrants such as reticulate vinylic polymers (such as crosslinked PVP), derivatives of starch and of cellulose such as sodium carboxymethyl-starch and sodium croscarmelose; wetting agents such as TWEEN 80 (Trademark registered by ICI of Americas for polysorbate) and sodium lauryl sulphate.

Suitable excipients and their amounts can be readily determined by the man skilled in the art according to the methods normally used in pharmaceutical technology. However, in the present invention, it is important to avoid excipients that would cause a significant decrease in tablet dissolution rate. Further, excipients must allow a good workability of the tablet.

In preparing the tablet of the present invention it is preferable to prepare a granulate with the mixture of ibuprofen, arginine and linear PVP, to mix to it the bicarbonate and the excipients, and then to compress.

When desired, the tablets can be film coated with a coating readily soluble in the gastric environment.

Suitable coatings can be prepared using conventional tablet coating compositions and methods. Preferred coatings include OPADRY II (sold by Colorcon; a mixture of hydroxypropyl methyl cellulose, pigments and a plasticizer), EUDRAGIT (sold by Rohm Pharma; a methacrylic acid ester polymer) and a combination of OPADRY II with saccharose.

The granulate can be prepared by direct granulation of the three components (ibuprofen, arginine and liner PVP) in the desired amounts or, after a first granulation of arginine with melted ibuprofen, by granulating a second time with linear PVP.

Both granulates obtained according the above described methods are then screened, dried,

combined with bicarbonate and any selected excipient(s) in the desired amounts and compressed in suitable moulds for obtaining the desired tablets which can then be film coated, if desired.

In addition to good handling and good workability, the tablets of the present invention provide complete dissolution of the active ingredient in about 10 minutes or less. Consequently the release is faster with respect to the commercially available ibuprofen based analgesic tablets (see example 5).

Generally, linear PVP is considered a binder at the amounts used in the present invention, and would be thus expected to inhibit dissolution or have little or no effect on dissolution.

With the aim to better illustrate the present invention the following examples are now given.

Example 1

Method for the preparation of the granulate of ibuprofen, arginine and linear PVP

Into an Erweka planetary mixer equipped with a thermostatic jacket bowl the entire quantity of ibuprofen was charged and melted at a temperature of 80°C under continuous stirring.

After all ibuprofen was entered, arginine, PVP and boiling water were added in that order.

After about 10 minutes of continuos stirring a creamy mass was obtained which was slowly cooled down to room temperature thus obtaining a solid granular mass.

Drying was completed by placing the granulate in a whirlpool static oven regulated at a temperature of 45°C for about 15 hours.

An alternative procedure involved preparing the ibuprofen and arginine granulate, to which powdered linear PVP was added and a second granulation of the mixture with cold water was carried out. The wet granulate obtained was dried in a whirlpool static oven. The alkaline bicarbonate and the excipients were then added.

Example 2

Alternative method for the preparation of ibuprofen, arginine and linear PVP granulate

Into a fast granulator water and arginine were sequentially introduced. When the arginine was partially dissolved, ibuprofen and linear PVP were added in sequence, and the mixture warmed under continuous stirring for about 30 minutes to obtain a creamy mass.

The creamy mass was then dried under vacuum for about 50 minutes.

At the end of drying the obtained mass was screened through an oscillating granulator equipped with a 1.5 mm sieve.

To the obtained granulate, bicarbonate and the excipients were then added.

The above described granulation method was also used in the preparation of an ibuprofen-arginine granulate to which powdered linear PVP was subsequently added.

The resulting mixture was granulated with cold water and the wet granulated product was dried in a static oven or directly into the granulator. The bicarbonate and the excipients were then added.

Example 3

Preparation of tablets

The granulate containing ibuprofen-arginine and linear PVP, obtained according to the procedure described in the example 1 or in the example 2, and to which bicarbonate and the excipients were added, was compressed to the desired weight.

Example 4

By operating according to the procedure described in the example 3, the tablets whose composition is reported in the following table 1 were prepared.

Table 1

Compositions according to the invention

	Tablets (mg)						
Ingredients	A	B	C	D	E	F	G
Ibuprofen	200	200	200	200	200	400	400
Arginine	185	185	185	185	185	370	370
PVP K90	5.4	5.4	5.4	5.4	5.4	10.8	10.8
Sodium bicarbonate	20	20	20	15	20	40	40
Microcrystalline cellulose	156			156	141	103	
Lactose		156					103
Dicalcium phosphate			156				
Sodium croscarmelose				30			
Sodium carboxymethyl starch			30				50
Reticulate PVP	30	30			30	50	
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	5.0	5.0
Colloidal silica	0.6	0.6	0.6	0.6	0.6	1.2	1.2
Tablet total weight (mg)	600	600	600	600	600	980	980

Example 5

Determination of the dissolution rate of tablets of the present invention

Determination of the dissolution rate was carried out by applying the method described in the U.S. Pharmacopeia XXIII, NF XVII, supplement No. 5.

Into a dissolution bath a solution of pH 7.2 phosphate buffer was charged and the liquid was thermostated at a temperature of 37°C.

The tablet to be checked was then charged and under continuous stirring by paddle at 50 rpm, the amount of ibuprofen in solution, expressed in percentage released as a function of time, was measured.

The tablets of the invention had an excellent dissolution rate in comparison with commercially available tablets containing the same amount of ibuprofen.

As an example, the ibuprofen contained in tablet A (see table 1) was completely in solution in 10 minutes according to the above described test, while a tablet of MOTRIN® (Upjohn) and one of ANTALGIL® (Jannsen-Cilag), containing the same amount of ibuprofen of tablet A, showed the release of a percentage of ibuprofen in solution of about 45% and 65% respectively, after 10 minutes.

It was necessary to wait at least 30 minutes before observing complete dissolution of the ibuprofen contained in the MOTRIN® and ANTALGIN® tablets.

Claims

1) An analgesic composition comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen.

2) A fast dissolving tablet comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen and including also normal excipients useful for the preparation of tablets.

3) A tablet according to claim 2, wherein the ibuprofen is present in an amount of from 100 to 400 mg.

4) A tablet according to claim 2, wherein the ibuprofen is present in an amount of from 200 to 400 mg.

5) A tablet according to claim 2, wherein arginine is present in an amount of from 1.1 to 1.3 moles per mole of ibuprofen.

6) A tablet according to claim 5, wherein the arginine:ibuprofen molar ratio is 1.2:1.

7) A tablet according to claim 2, wherein the linear PVP has an average K value of from 25 to 90.

8) A tablet according to claim 7, wherein the linear PVP is PVP K90.

9) A tablet according to claim 2, wherein the alkaline bicarbonate is sodium or potassium bicarbonate.

10) A tablet according to claim 2, wherein ibuprofen is present in an amount of 200 or 400 mg, arginine is present in an amount of 1.2 moles per mole of ibuprofen, the linear PVP is PVP K90 and the alkaline bicarbonate is sodium bicarbonate.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 99/04874

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/19 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 09763 A (ISP INVESTMENTS INC.) 27 May 1993 (1993-05-27) page 1 claims 1-5	1-10
Y	GB 2 279 250 A (ZAMBON S.P.A.) 4 January 1995 (1995-01-04) examples 9,10	1-10
A	WO 97 30699 A (THE BOOTS COMPANY PLC) 28 August 1997 (1997-08-28) claims 1-15 examples 24-26	1-10
A	DE 36 38 414 A (ZAMBON S.P.A.) 21 May 1987 (1987-05-21) & US 4 689 218 A cited in the application	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1999	05/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 99/04874

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 602 141 A (ZAMBON SPA) 5 February 1988 (1988-02-05) & US 4 834 966 A cited in the application	1-10

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 99/04874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9309763 A	27-05-1993	US 5262171 A	16-11-1993
		AU 3136293 A	15-06-1993
GB 2279250 A	04-01-1995	IT 1264856 B	17-10-1996
		BE 1007194 A	18-04-1995
		CA 2125643 A	22-12-1994
		CH 687850 A	14-03-1997
		DE 4420856 A	22-12-1994
		DK 72594 A	22-12-1994
		ES 2099021 A	01-05-1997
		FR 2706892 A	30-12-1994
		HU 9500467 A	28-09-1995
		JP 7101855 A	18-04-1995
		NL 9401005 A	16-01-1995
		NO 942343 A	22-12-1994
		SE 9402157 A	22-12-1994
		US 5500226 A	19-03-1996
		US 5645857 A	08-07-1997
WO 9730699 A	28-08-1997	AU 1793797 A	10-09-1997
		BG 102744 A	31-05-1999
		CA 2246344 A	28-08-1997
		CN 1215989 A	05-05-1999
		CZ 9802617 A	11-11-1998
		EP 0881899 A	09-12-1998
		HU 9901454 A	30-08-1999
		NO 983825 A	20-10-1998
		PL 328465 A	01-02-1999
		SK 114298 A	11-01-1999
DE 3638414 A	21-05-1987	IT 1209667 B	30-08-1989
		AT 395372 B	10-12-1992
		AU 6509886 A	14-05-1987
		BE 905737 A	12-05-1987
		CA 1276113 A	13-11-1990
		CH 674934 A	15-08-1990
		FR 2590893 A	05-06-1987
		GB 2189994 A,B	11-11-1987
		GR 862697 A	10-03-1987
		IE 59055 B	15-12-1993
		JP 7061941 B	05-07-1995
		JP 62149615 A	03-07-1987
		MX 9203170 A	01-07-1992
		NL 8602870 A,B,	01-06-1987
		US 4689218 A	25-08-1987
FR 2602141 A	05-02-1988	IT 1197038 B	25-11-1988
		AT 394945 B	27-07-1992
		AU 595342 B	29-03-1990
		AU 7554087 A	04-02-1988
		BE 1002109 A	10-07-1990
		BG 60832 B	30-04-1996
		CA 1286992 A	30-07-1991
		CH 673394 A	15-03-1990
		DE 3725176 A	04-02-1988
		GB 2193093 A,B	03-02-1988
		GR 871197 A	04-12-1987
		IE 60276 B	29-06-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/EP 99/04874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2602141 A		JP 2585005 B	26-02-1997
		JP 63041420 A	22-02-1988
		MX 9203167 A	01-07-1992
		NL 8701729 A	01-03-1988
		US 4834966 A	30-05-1989
		ZA 8705397 A	01-02-1988